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| **Opportunistic Fungal Infections: T-cell mediated immune deficiency – Generally are YEASTS**   * **T cell mediated def (AIDS, hypergammaglobulinemia, DiGeorge)🡪 cryptococcosis and pneumocytosis + superficial/mucosal candidiasis** | | | | |
| **Name** | **Diagnosis** | **Symptoms** | **Pathogenesis** | **Treatment** |
| ***Cryptococcus neoformans***  *neoformans –* throughout USA (**pigeon shit)**  *gatti –* restricted to warmer areas (**Eucalyptus tree** -British Columbia)  Two diverse strains mated 🡪 new **true pathogenic** strain  Cryptococcus  Encapsulated Yeast in vivo and in vitro | * Grows as an **encapsulated budding yeast** ***in vitro* and *in vivo***   Anamorph: Budding yeast  Telomorph: Basidiospores – filamentous  🡪 Not environmentally controlled  🡪 Not dimorphic   * Suspect in patients with **T-cell mediated immune deficiency, especially:**   + AIDS   + High dose steroids   + Sarcoid treatment   + Chemotherapy patients | * Pathogenic in normal host, but especially in Immunocomp host * Pulmonary infection initially ± dissemination * Lung disease may be severe, but **usually inapparent**   + Yeasts/basidiospores are infectious * Dissemination from lungs usually to **CNS** and **skin** via blood and lymph   + Can get meningitis   + Gelatinous growth in meninges will show capsular polysaccharide   **Cerebromeningeal disease**   * Fever, headaches, meningismus * Visual disturbances * Abnormal mental status * Seizures   Meningitis: most common   * Headache * Visual changes * Changes in personality * Increased intracranial pressure * + or – fever   Pulmonary:   * variable asymptomatic-bilateral pneumonia * Nodular infiltrates * Rarely cavitation   CNS Parenchyma (cryptococcoma):   * Rare neoformans/grubii * Var. gattii in competent hosts (it’s uncommon)   Dissemination:   * Skin lesions * ocular including chorioretinitis * osseous | * Inhalation🡪ingested by macros🡪capsule inhibits phagocytosis and suppresses cellular/humoral immunity   Virulence factors   * Acidic capsular polysaccharide   + Negative charge 🡪 repulse   + Antiphagocytic   + T-Independent antigen   + Observable in India Ink * Phenoloxidase   + Oxidizes phenolics to form a deep pigment similar to melanin   + Valuable in invasion of CNS * Melanin cell wall: responsible for neurotropism   Host Defense   * Alveolar macros * Inflamm phagocytic cels * T and B cell rxn * Host immunity is critical, esp T cells | * Fatal if untreated * 2 weeks Amphotericin B + flucytosine * 8+ weeks of fluconazole * Therapeutic LP (lumbar punctures) may be necessary to decrease intracranial pressure |
| **Labs** |
| Culture: **Bird seed agar**   * **Capsule stains with mucin stain (Mayer mucicarmine)** * **Blood; CSF**   **Microscopy: Gram or India ink**   * Grows as **dark** colony b/c phenoloxidase * Candida albicans grows **white**   Rapid antigen detection test   * **Antigen Assay serum/CSF: polysaccharide capsule** * **Latex agglutination test for capsule** * Especially useful for CSF (meningitis) |
| ***Pneumocystis jirovecii***  pcpcysta.jpg Cysts  pcp_stain2.jpg | * Major cause of pneumonia in **AIDS** * Thought it was a protozoan initially | * Rapid progression of pneumonia over matter of days * Respiratory tract main portal of entry → pneumonia * Pneumonia most common * Lymph nodes, spleen, BM, liver, GI tract, GU tract * Both 1airy infection and reactivation * Slowly progressive * Shortness of breath (on exertion); fever; dry cough   **Epidemiology**   * AIDS: CD4 <200 * Transplant * Other immuno-compromised hosts: T cell immunity | * Human/animal strains not cross contagious * Interferes with oxygen diffusion in alveoli | * Prophylactic treatment when CD4 is >200 ul w/ TMP-SMX * **Tx: Trimethoprim-sufamethoxazole or pentamidine if person had sulfa allergy** |
| **Labs** |
| * **CANNOT be cultured** * Diffuse interstitial infiltrates – chest x-ray   **Broncioalveolar lavage**   * **Silver/Giemsa stain: trophic forms** * GMS stain: specific cyst wall * Immunofluor: tropic and cyst wall * Improved with Calcoflur * **free trophic forms** * **sporocysts--cyst (4-8 intracystic bodies)** |
| ***Micosporidiosis***  Micrsp_EM1 Coiled polar tubules  \*\*MOST COMMON SPP. ARE ENCEPHALITOZOON  Description: Spore ultrastructure  Pt: Portion of coiled polar tubule  Ex: Electron dense exospore  En: Electron lucent endospore  Pv: Posterior vacuole | * Found in **AIDS**. **Probably a parasite** | * Severe GI disease * Lung disease * Other sites –ocular * Mimics cryptosporidium (ie, diarrhea) | * Multiplies **intracellularly**🡪 either in cytoplasm (E. hellem---spres present in BAL from patient w/ AIDS) or in paprasitophrous vacuole (E. intestinalis) * **Coiled polar tubule helps it enter cells** * Spores can survive for long periods in the environment | * Albendazole (antiparasitic agent—blocks glucose uptake by interrupting microtubular function) |
| **Labs (look under light microscope)** |
| * **Modified gram stain** of diarrhea shows very tiny “spores” – improved with  **Calcofluor white and modified acid fast stains** * **Description: Microsporidian spores stained with Quick Gram Chrmomotrope** * Electron Micrograph: see coiled **polar tubule** – helps invade cell   + Also can see electron dense exospore, electron lucent endospore, and posterior vacuole) * Spore wall contains chitin (keep antimicrobials from working well) |
| ***Candida albicans***  **SuperficialSkin/mucosal infection ONLY**  \*\*don't need to be immunosupp to see this infection Screen Shot 2012-10-22 at 12  \*\*ALSO SEE BELOW FOR MORE INFO AND PICS—under invasive candida  chronic mucocutaneous candidiasis | * **Produces pseudohyphae and germ tubes—can also do phenotypic switching (adjusts to diff environments of the body)** * Yeasts are colonizers of GI/GU tract * Suspect in patients with **T-cell mediated immune deficiency, especially:**   + **Diabetes**, T-cell deficiency     - Patients with uncontrolled DM and poorly fitting dentures get this * Common In areas where skin remains wet:   + Mouth corners (Dentures), between fingers, By ball sac with satellite lesions, and can see it in baby diaper rash * **Sabouraud's dextrose agar shows typical cream coloured, smooth surfaced, waxy colonies** | Clinical Features   * Skin/soft tissue infection   + T cell mediated immunity important   + Diabetes   + T cell def—AIDS * **Mucosal infection (oral-thrush/esophageal/vaginal)**   + **Candida esophagitis is AIDS defining in HIV pos**   + Release of cytokines from Th1 cells stimulates epidermal growth   + Severe esophageal candidiasis in AIDS 🡪 ulcerative erosions and barium leak   + **Vaginitis** ---with **cottage cheese like discharge** * Bloodstream (central line for long period of time) * Others (endocarditis, CNS—meningitis common in preterm neonate) * Deep seated infections—PMN’s are an essential defense & neutropenia is a major predisposing factor   + Often see skin lesions🡪 Usually in kidney (medulla has tiny vessels) and eye (also has tiny vessels) * ↑inflammation/erosion vs. *Malassezia* | Routes for invasion   * Normal flora of GI so may penetrate through wall---when GI is inflamed its common to leak through wall (Chron’s or IBS or patient getting chemo—neutropenic) * You see it in patients on antibiotics b/c you wipe away normal flora (skin) and can also see thrush (yeast infection of the mucous membrane lining the mouth and tongue) * Release of cytokines from TH1 cells stimulates epidermal growth   Chronic Mucocutaneous Candidiasis   * Rare * Candida on dry skin and nails * Masses of Abs * Susceptibility is multifactorial   + T cell (anergy may be restricted to Candida)   + Zinc def   + Endocrinopathies * Diff spp (other than albicans) have diff pattern of sugar assimilation—species identification can be important for tx choices—some are resistant to fluconazole * **Highly flexible morphology** with filamentous forms binding different human proteins than do yeast forms. Filaments appear more invasive * **Phenotypic switching (more info below)** enhances capacity to change with environment * Serious skin and mucosal infections **do not cause** disseminated disease unless PMNs become dysfunctional | * Amp B if infection is bad * Fluconazole for local stuff   \*\*make sure you ID the spp. |

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| **Opportunistic Fungal Infections: Neutrophil immune deficiency – Generally are MOLDS**   * **PMN-mediated def🡪invasive asperfillosis, invasive zygomycosis, and invasive (deep seated/systemic) forms of candidasis** | | | | |
| **Name** | **Diagnosis** | **Symptoms** | **Pathogenesis** | **Treatment** |
| ***Aspergillus fumigates, flavus,  niger***  ***-*INVASIVE**  http://www.mycology.adelaide.edu.au/images/Nov1.gif aspergill conid.jpg  Septate hyphae, branching at 45° | * **Mold** producing abundant **blastoconidia** on **conidiophores** * On composts and rotting plant materials * Septate branching hyphae; angiotrophic * *Fusarium* mimics growth pattern but is rare (Contact lenses) * More and more seen post bone marrow transplant * Spore🡪germ tube🡪hyphae/mycelium | Allergic reactions   * Bronchopulmonary form:   + Spores germinate in bronchioles and begin to grow   + Allergic mucus response leads to plugging of bronchioles. ABs ↑↑   + Significantly reduced lung capacity   + Asthma   + Pulmonary infiltrates   + Eosinophilia   + Elevated IgE   + Hypersensitivity Aspergillus Ag * Allergic sinusitis:   + Eosinophilia   + Hypersensitivity Aspergillus Ag   + Nasal obstruction   + Discharge   + Headache   Colonization   * Sinuses / Lower airways * Obstructive bronchial aspergillosis   + Usually other underlying disease: CF, COPD   + Bronchial plugs   + No tissue injury   + No treatment necessary * Fungal ball (aspergilloma)   + Pre-existing cavity/sinus   + No treatment unless hemorrhage → surgery   Locally invasive aspergillosis   * Limited forms   + Necrotizing pseudomembranous bronchial aspergillosis   + Chronic necrotizing pulmonary aspergillosis * Underlying pulmonary disease/usually steroids * Chronic, locally destructive * Treatment – surgical / medical   Invasive aspergillosis   * Severe ICH (immune compromised hosts) neutropenic /steroids → macrophage / T cell dysfunction) * Invasive pulmonary aspergillosis (IPA)   + Fever   + Infiltrates   + Chest pain / hemoptysis   + Mortality over 70% * Hematogenous disseminated   + Angioinvasion   + Brain, Heart, Kidney, GI, Liver, Spleen | * Inhaled conidia bind fibrinogen / laminin alveolus * Conidia germinate * Macrophages ingest/kill conidia * Neutrophils adhere to/kill hyphae * Hyphal forms secrete proteases / invade epithelium * Vascular invasion → thrombosis * Predisposed: Neutropenia/impaired neutrophils   Epidemiology   * Worldwide * Conidia ubiquitous in air, soil, decaying matter * Transmission: * Inhaled (constantly) * Transdermal (tape/bandages) * Outcome depends on host factors | * **Amphotericin B (lipid) (*A. terreus* R)** * **Voriconazole** |
| **Labs** |
| Culture: Grows very well at 45°C   * Culture: hyaline molds (black, brown, green, yellow) * Grow: branched, septate hyphae (PAS, GMS (silver) produce conidial heads when exposed to air (culture/tissue) * Hyphae: uniform width, regular septations tree-like branching; branches acute angles (45) conidial heads rarely in tissue (may be in cavities)   CT scan: **Air crescent in lungs** (except in people with absolutely no neutrophils)  Biopsy  Won’t see in blood sample usually! |
| **Invasive *Zygomycetes***  http://micol.fcien.edu.uy/atlas/rhi02.jpg  Sporangiospores  http://labmed.ucsf.edu/education/residency/fung_morph/fungal_site/thumbnails/rhizopus.7ofw4.jpg  Aseptate hyphae | * Anamorphs: **sporangia & sporangiospores** * Germinate to form hyphae/mycelium   + **Wide, aseptate, irregular hyphae—they look swollen**   + Hyphae are angiotropic * They like and spread through BV**’s** * **Rapidly growing molds** * Much rarer than *Aspergillus* * Can get coinfection with *Aspergillus* * Neutropenia is main predisposing factor🡪 macrophages are better at controlling these fungi | Zygomycosis (Mucormycosis)   * Systemic disseminated zygomycosis * **Neutropenia** is main predisposing factor (see it in AML w/ chemotherapy) * Much rarer than aspergillosis—macrophages better able at controlling these fungi * Infection usually via lung with dissemination, but invasion can enter through other routes including GI or via contaminated skin wounds   Rhinocerebral zygomycosis   * Infection via nasal turbinates and sinuses into CNS (lethal in brain) * **ONLY in uncontrolled diabetics with ketoacidosis** * Damage around orbit * Can see black necrotic discharge in sinuses palate   Bone marrow transplant recipients   * Get zygomacosis when given **voriconazole**/**posaconazole** prophylactically for *Aspergillus* * **Zygomycetes generally resistant to azoles** | * **Usually via lung with dissemination, but can occur via GI and wounds** * Hyphae are angiotrophic * **Iron stimulates growth—so pt on cytotoxic chemo that has iron overload from multiple transfusion you can see this** * Rapidly growing molds * Ubiquitous * Behaves like aspergillosis🡪**angio-invasive & can disemm and cause tissue destruction**   Multiple Genus   * Rhizopus * Mucor * Rhizomucor * Absidia * Cunninghamella | * **Resistant to azoles, including resistance to newer azoles:** Voriconazole/ Posconazole * **MUST USE amphotericin B** * **Surgical Debridement** |
| ***Candida albicans***  Invasive  Deep-seated, systemic  Screen Shot 2012-10-22 at 12  Screen Shot 2012-10-22 at 12germ tube | * **See BOTH yeasts and hyphae in tissues** also in Tinea Versicolor (*Malassezia*) but these are noninflammatory/localized   Culture (Sarabound agar)   * **On low Glucose and pCO2↑ yeast converts to filamentous form** * Yeast: **Pseudohyphae** (Elongated budding yeast) * Filamentous: **Chlamydospore\*\***   **🡪 Diagnostic for *Candida albicans***  (and *Candida dubliniensis)*  **Germ Tube test** (Mix *Candida* w/serum)   * *C. albicans* (and *C. dubliniensis*)will form germ tubes | * Serious skin and mucosal infections **do not** cause disseminated disease unless neutropenia develops   Chronic Muscocutaneous Candidiasis   * + See above | * **NOT respiratory route of inf’n** * **Infect via GI and indwelling catheters** * Normal Flora of mucosal surfaces * Dissemination to eye, vitreous fluid, heart   **Phenotype switching** (10-5)   * Not a product of mutation * Switches morphology and metab * Enhances ability to thrive in different environments * Can develop resistance to drugs * Can develop antiphagocitosis | * Some species resistant to fluconazole 🡪 thus important to identify species; based on **patterns of sugar assimilation** |